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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Barry Eisenstein	Art Unit:	1618
Serial No.:	10/652,799	Examiner:	Blessing M. Fubara
Filed:	August 29, 2003	Customer No.:	21559
Title:	METHODS AND REAGENTS FOR TREATING INFECTIONS OF <i>CLOSTRIDIUM DIFFICILE</i> AND DISEASES ASSOCIATED THEREWITH		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. CHARALABOS POTHOUKAKIS

I declare:

1. I, Charalabos Pothoulakis, hold an M.D. from Aristotelian University of Thessaloniki Medical School in Greece. I am currently a Professor of Medicine in the Gastroenterology Department at Beth Israel Deaconess Medical Center, Harvard Medical School. I am also the director of the Gastrointestinal Neuropeptide Center in the Gastroenterology Division at Beth Israel Deaconess Medical Center. I have been working in the field of infectious diseases, particularly bacterial infections of the small intestine

and colon, for over 20 years. I have over 80 publications in peer-reviewed journals on the subject of *Clostridium difficile* infections and *C. difficile*-associated disease. I am considered an expert in the field of gastrointestinal infections.

2. *C. difficile* is a gram-positive anaerobic bacterium that is now recognized as the major causative agent of inflammation of the colon (colitis) and diarrhea. *C. difficile* infection represents one of the most common hospital infections around the world causing approximately three million cases of diarrhea and colitis per year in the United States alone. *C. difficile* infections are most prevalent in hospitals or chronic care facilities, where *C. difficile* is generally present in the environment and patients frequently receive antibiotics. The widespread use of antibiotics, particularly broad spectrum antibiotics, in these facilities promotes susceptibility to *C. difficile* because antibiotic therapy results in alterations of the beneficial bacteria normally found in the colon, allowing for colonization by *C. difficile*, or its spores, that are present in the environment.

3. *C. difficile* is a particularly difficult organism to treat because antibiotics, typically used to treat bacterial infections, can actually contribute to *C. difficile*-associated disease by altering the environment in the colon to allow *C. difficile* to flourish. Even if the antibiotic used for therapy is effective initially, there is a high incidence (15 to 20%) of relapsing diarrhea following an initial response, and this relapsing *C. difficile* infection

is one of the most difficult infections to treat because, in this case, any antibiotic therapy has the potential to disrupt the normal environment of the colon and further encourage the growth of the *C. difficile* organism.

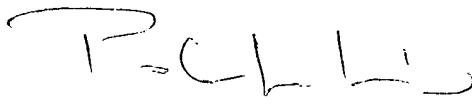
4. Most, if not all, antibiotics can alter the environment in the colon in a way that allows *C. difficile*, if present in the environment, to flourish.

5. I have looked at the list of 141 antibacterial agents listed in Chamberland et al., U.S.P.N. 6,114,310, and it is my expert opinion that the vast majority of these antibacterial agents would contribute to *C. difficile* infections by disrupting the normal environment of the colon as described above.

6. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

06/30/05

Date



Dr. Charalabos Pothoulakis